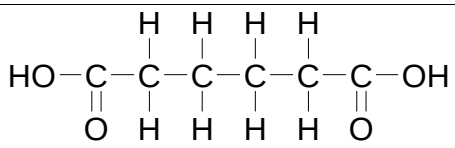
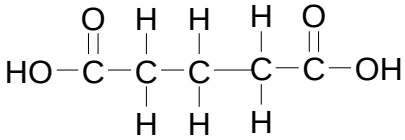
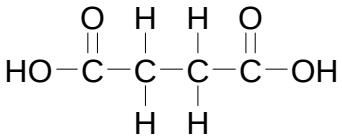
10-July-2001

ROBUST SUMMARY FOR DICARBOXYLIC ACID CATEGORY

Summary

Identification of a structure based category

The alkane dicarboxylic acid category is composed of linear alkanes with a common function group, carboxylic acid, at each end of the alkane chain. This category is composed of discrete materials that change by an increase in carbon number from an addition of CH_2 in the alkane chain between the carboxylic acid groups. The total carbon chain length is between four and six carbons. Dicarboxylic acids included in this group are succinic acid (C4), glutaric acid (C5), and adipic acid (C6). Structures of these acids are presented below.

Chemical Name	CAS Registry Number	Structure
Hexanedioic acid (Adipic Acid)	124-04-9	
Pentanedioic acid (Glutaric Acid)	110-94-1	
Butanedioic acid (Succinic Acid)	110-15-6	

The terminal carboxylic acids and limited chain length provide similar structure activity relationships with these materials. The boundaries for this category were placed on C4 to C6 dicarboxylic acids, as these materials are products of adipic acid manufacture from cyclohexanol. In addition to information on the discrete materials, data exists and will be presented on a mixture of the dicarboxylic acids (AGS mixture) to lend overall support to the alkane dicarboxylic acid category. Finally, in the data summaries information will be presented that indicate these materials share similar physical chemical properties, environmental fate characteristics, ecotoxicity, and mammalian toxicity.

Scientific literature was searched and summarized. Data were identified for materials in the category, as well as data on the mixture of member materials (Table 1). A majority of the SIDS endpoints were covered for the individual materials, as well as the category. Each study on category materials was evaluated for adequacy. Robust summaries were developed for each study addressing specific SIDS endpoints. Summaries were also developed for studies either considered not adequate but provided information of

relevance for hazard identification and evaluation, or covered non-SIDS endpoints (Appendices A-D).

Table 1: Matrix of Available and Adequate Data for Dicarboxylic Acid Category

	Adipic Acid	Glutaric Acid	Succinic Acid	AGS Mixture
PHYSICAL/CHEMICAL CHARACTERISTICS				
Melting Point	√	√	√	√
Boiling Point	√	√	√	√
Vapor Pressure	√	√	√	√
Partition Coefficient	√	√	√	–
Water Solubility	√	√	√	√
ENVIRONMENTAL FATE				
Photodegradation	√	√	√	–
Stability in Water	√	√	√	–
Transport (Fugacity)	√	√	√	–
Biodegradation	√	√	√	√
ECOTOXICITY				
Acute Toxicity to Fish	√	√/–	√/–	√
Acute Toxicity to Invertebrates	√	–	√	√
Acute Toxicity to Aquatic Plants	√	√/–	√/–	√
MAMMALIAN TOXICITY				
Acute Toxicity	√	√	√	√
Repeated Dose Toxicity	√	√	√	√
Developmental Toxicity	√	√	–	–
Reproductive Toxicity	–	–	–	–
Genetic Toxicity Gene Mutations	√	√	√	√
Genetic Toxicity Chromosomal Aberrations	√	√	√	√

√ = Data are available and considered adequate.
– = No data available.
√/– = Data are available, but considered inadequate.

Evaluation of Data Matrix Patterns

The available adequate data were broken out by discipline (physical chemical, environmental fate, ecotoxicology, and mammalian toxicology). These comparisons were conducted to determine if a pattern existed among the materials and to determine if additional testing needed to be conducted to complete the data set for the category. In general, the most striking pattern across the group of materials is their low toxicity. This applies to both mammalian species, as well as aquatic organisms.

All three alkane dicarboxylic acids have roughly equivalent physical chemical properties (Table 2). Further these properties follow a general trend with succinic acid (C4) having a lower boiling point, vapor pressure, and Kow, and higher density, melting point, and water solubility than adipic acid (C6). Glutaric acid has physical chemical properties that generally fall within the values for succinic and adipic acids. Thus a true trend for the alkane dicarboxylic acid category exists.

Table 2: Physical and Chemical Characteristics

	Adipic Acid	**Glutaric Acid**	**Succinic Acid**	**Dicarboxylic Acid Mixture**
Physical Appearance	White, odorless, crystalline powder	White crystalline solid	Colorless to white crystalline powder, odorless to carmel odor	Off-white solid, with a pungent odor
Molecular Weight	146.14	132.13	118.09	Not Applicable
Water Solubility	30 g/L at 30ºC	1600 g/L at 28ºC	83 g/L at 25ºC	350 g/L at 25ºC
Melting Point	152ºC	97.5-98ºC	185-187ºC	100-130ºC
Boiling Point	330.5ºC	302-304ºC	235ºC	300-330ºC
Vapor Pressure	3.18×10^{-7} mm Hg at 25ºC	2.88×10^{-6} mm Hg at 25ºC	1.9×10^{-7} mm Hg at 25ºC	4 mm Hg at 160ºC
Density	1.360 at 25º/4ºC	1.429 at 15º/4ºC	1.564 at 15º/4ºC	1.23 at 20ºC
Partition Coefficient (log Kow)	0.081	-0.29	-0.59	No Data

Ecotoxicity data are essentially equivalent for the category members (Table 3). The environmental fate data indicate all materials are readily biodegradable and do not bioaccumulate. Fugacity model prediction for the alkane dicarboxylic acids indicate these materials will act similarly in regards to partitioning in the environment. Modeled data shows that all 3 test materials are essentially the same in terms of partitioning, with more material partitioning to the soil, and to a slightly lesser extent to water, with virtually none going to air or sediment.

Table 3: Ecotoxicity

	Adipic Acid	**Glutaric Acid**	**Succinic Acid**	**Dicarboxylic Acid Mixture**
Bioaccumulation *	Low BCF = 0.68	Low BCF = 3.162	Low BCF = 0.21	No Data
Biodegradation	Readily Biodegradable	Readily Biodegradable	Readily Biodegradable	Readily Biodegradable
Fugacity*	Air <0.001% Water 42.4% Soil 57.5% Sediment 0.06%	Air <0.001% Water 42.6% Soil 57.3% Sediment 0.064%	Air <0.001% Water 42.7% Soil 57.2% Sediment 0.06%	No Data
* Modeled data.				

Aquatic toxicity of the alkane dicarboxylic acid category is generally low (Table 4). Acute toxicity to fish for adipic and glutaric acids are similar. Data for succinic acid, although not definitive, indicate that the LC_{50} for succinic acid is in the same general order. This conclusion is also supported by data generated for the mixture of the three dicarboxylic acids. Information with *Daphnia* indicate results for adipic and succinic acids in the same order of magnitude. Finally, acute toxicity to algae indicate that dicarboxylic acids have similar toxicity in these organisms.

Table 4: Aquatic Toxicity

	Adipic Acid	**Glutaric Acid**	**Succinic Acid**	**Dicarboxylic Acid Mixture**
Toxicity to Fish (LC_{50} value)	97 mg/L (96-hour)	330 mg/L (24-hour)	>15 ppm (24-hour)	240-340 mg/L (96-hour)
Toxicity to Invertebrates (EC_{50} value)	85.7 mg/L (48-hour)	No Data	374.2 mg/L (48-hour)	>1000 mg/L (48-hour)

Toxicity to Algae (EC_{50} value)	26.6 mg/L (96-hour)	264 mg/L (72-hour)	120 mg/L	35 mg/L (96-hour)

In mammalian species the low toxicity is manifest in high lethal doses in acute studies, limited toxicity (body weight effects) in repeat dose studies, and no effects in teratologic evaluations (Tables 5 and 6). This is not unexpected as succinic acid is a component of carbohydrate metabolism in living systems, and the FDA regulates adipic acid as a GRAS (generally recognized as safe) component. It appears that the LD_{50} may be influenced by chain length as the C4 dicarboxylic acid, succinic acid, has a lower LD_{50} than glutaric (C5) and adipic (C6) acids. A similar relationship also exists in ocular irritation, where severity of response decreases with increasing carbon number. When tested in rabbits, adipic acid produced slight to mild skin irritation, and glutaric and succinic acids produced slight skin irritation. When tested in guinea pigs the mixture produced no to mild skin irritation. In dermal sensitization studies in guinea pigs, adipic acid and the mixture of the acids did not produce skin sensitization.

Table 5: Acute Mammalian Toxicity

	Adipic Acid	**Glutaric Acid**	**Succinic Acid**	**Dicarboxylic Acid Mixture**
Oral LD_{50} (rat)	5050 mg/kg	2750 mg/kg	2260 mg/kg	6829 mg/kg
Inhalation LC_{50} (rat)	> 7.7 mg/L	No Data	No Data	>0.03 mg/L
Dermal LD_{50} (rabbit)	> 7940 mg/kg	> 10,000 mg/kg	No Data	> 7940 mg/kg
Dermal Irritation	Slight to mild	Slight	Slight	No to mild
Eye Irritation	Mild to moderate	Moderate	Severe	Mild to severe
Dermal Sensitization	Not a sensitizer	No Data	No Data	Not a sensitizer

Repeated exposure studies in rats with adipic acid (2 years), glutaric acid (90 days), and succinic acid (90 days and 2 years, tested as the sodium salt, which is appropriate since on contact with water in living systems it dissociates to the acid form), as well as the mixture of the acids (90 days), have indicated a low degree of toxicity. A low degree of toxicity was also seen in a repeated exposure study (90 days) with glutaric acid in dogs. Concentrations of 1-2% of the individual acids, and 3% of the acid mixture were well

tolerated. Higher concentrations of all 4 test substances were associated with a depressed rate of weight gain. No specific target organ was identified for any of the individual acids or the AGS mixture.

Developmental toxicity studies have been conducted for glutaric and adipic acids in both rat and rabbit (Table 6). These studies resulted in no adverse effects on pregnancy and no embryotoxic or teratogenic effects. It is reasonable to assume that this category does not pose a developmental toxicity hazard.

Evaluation of reproductive toxicity for the alkane dicarboxylic acid category cannot be conducted with currently available data (Table 6). No studies have been conducted to examine the effects of any of these materials on male or female fertility. Histopathological evaluations of the gonads were conducted in some of the repeated dose studies, but were not sufficient to eliminate the possibility of an effect. Based on the similarity of results in acute and repeated dose studies for the alkane dicarboxylic acids, it is anticipated that effects on fertility would be similar. As such it is proposed to evaluate the reproductive effects of adipic acid in an OECD Guideline 422 reproductive toxicity screen.

Table 6: Repeated Dose, Developmental, and Reproductive Toxicity

	Adipic Acid	**Glutaric Acid**	**Succinic Acid**	**Dicarboxylic Acid Mixture**
Repeated Dose Toxicity (NOAEL)	1% in a 2-year study	1-2% in a 90-day study	1.25% in a 90-day study 1% in a 2-year study	3% in a 90-day study
Developmental Toxicity	Not teratogenic	Not teratogenic	No reliable data	No Data
Reproductive Toxicity	No effect on reproductive organs in repeated exposure studies	No effect on reproductive organs in repeated exposure studies	No reliable data	No effect on reproductive organs in a repeated exposure study

Genetic toxicity data are similar between the three acids, supporting a category approach (Table 7). Neither succinic, glutaric, nor adipic acids induce mutations in bacteria, as is the case with the mixture. Similar responses were seen with the 3 diacids and clastogenic activity. Adipic acid was inactive *in vitro* and *in vivo*. Succinic acid was inactive *in vitro*; glutaric was inactive *in vivo,* and essentially inactive *in vitro* (2 assays reported negative results and 1 assay reported positive results). It can be reasonably assumed that succinic acid will be inactive *in vivo* and glutaric inactive *in vitro*. The mixture of the

acids was inactive in point mutations assays in *Salmonella*, unscheduled DNA synthesis (UDS) in rat hepatocytes, and in the HGPRT assay. Somewhat surprisingly, the mixture of the acids was genotoxic in an *in vitro* Chinese hamster ovary (CHO) clastogenicity study. The reason for this response is not known. The mixture was, however, inactive *in vivo*. Taken collectively, it can be concluded that these test substances are inactive for mutagenic and clastogenic effects.

Table 7: Genetic Toxicity

	Adipic Acid	**Glutaric Acid**	**Succinic Acid**	**Dicarboxylic Acid Mixture**
Mutagenic	No	No	No	No
Clastogenic	No	No	No	No

Overall, the toxicologic database for the individual acids and the mixture is relatively complete, and the information available does not suggest a high level of concern. The database could be enhanced by investigating reproductive toxicity. Table 8 lists the proposed test plan for the dicarboxylic acid category. The shaded cells represent those SIDS endpoints for which testing was recommended.

Table 8: Alkane Diacids Proposed SIDS Test Plan

	Adipic Acid	Glutaric Acid	Succinic Acid	AGS Mixture
Reproductive Assessment	-	-*	-*	-

- = No data available.
* = Evaluation of the test substance will be considered based upon the results obtained from the study performed with adipic acid.

Once the reproductive screen on adipic acid is completed the results will indicate if additional testing is needed. If no adverse effects on reproductive function are determined, no additional testing will be conducted. If reproductive function is adversely affected, succinic/glutaric acids will be considered for evaluation to determine if these effects occur across the entire range of alkane dicarboxylic acids.

Exposure Assessment

Dibasic Acid (DBA) is a by-product manufactured in the production of adipic acid at several domestic and regional facilities. Glutaric and succinic acids are non-commercialized by-products of this process. Approximately 94% of the volume of DBA produced is as adipic acid. Approximately 4.25% of the dibasic acid mixture is converted to dibasic esters by esterification of the acid moieties with methanol, either on site or by toll manufacturers. Approximately 1.2% of the DBA production is burned as

fuel at manufacturing sites and the remaining 0.55% is sold to customers or distributors for use as corrosion inhibitors and as a pH buffer for lime and limestone SO_2 scrubbers. All sites that produce and use DBA have safety, health, & environmental practices and procedures in place and utilize engineering controls, environmental controls, and personal protective equipment to manage the risk of exposure above recommended limits. The toll manufactures also have procedures, practices, and controls in place to manage the risk of exposure, and no sites or customers have reported any SHE incidents from the handling of DBA. The major manufacturers of DBA practice Responsible Care® and assess the ability of potential toll manufacturers and customers to safely handle DBA prior to commencing a commercial relationship. This assessment includes reviews and audits of PPE (personal protective equipment), safety equipment and procedures, structural integrity, and safety practices.

DBAs are primarily the by product of commercial production of adipic acid, an industrial intermediate for the production of Nylon 6,6 for use in fibers, engineering resins, films, and monofiliments. Other applications for adipic acid include flue gas desulphurization, adhesives, and food additives. Adipic acid is generally recognized as safe (GRAS) under 21 CFR 184.1009 when used in foods at levels not to exceed current good manufacturing practice in accordance with 21 CFR 184.1b1.

Concerns with adipic acid focus on physical handling of the product. When dispersed as a dust, adipic acid is subject to normal dust explosion hazards. The minimum ignition energy (MIE), a measure of dust explosivity, is 5 mJ. Tests show that unloading 907 kg (2000 lb) bulk bags of adipic acid can generate voltage levels necessary to constitute a spark hazard. The major producers of adipic acid practice Responsible Care® and follow its distribution management practice.

The sites handling DBA and adipic acid can have from 250 to 2000 personnel (construction, contractor, and plant employees). The area where the substances are manufactured will have from 2 to 5 operators during normal operations and from 10 to 60 people during a shutdown or major construction activity. The DuPont Acceptable Exposure Limit for adipic acid is 5 mg/m^3, 8- and 12-hour TWA. The ACGIH Threshold Limit Value is 5 mg/m^3, 8-hour TWA, and the Workplace Environmental Exposure Level is 5 mg/m^3, 15-minute TWA. OSHA has not established a Permissible Exposure Limit.

Exposure Groups

Data are presented below on various occupational exposures to alkane dicarboxylic acids. As the majority of alkane dicarboxylic acids are produced as site limited intermediates, exposure to these materials are limited. Little exposure to adipic acid, glutaric acid, or succinic acid vapor occurs to manufacturing personnel. Exposure to adipic acid, the one alkane dicarboxylic acid with large commercial applications, during the loading of hopper cars and QA/QC in the process lab, is below exposure standards.

Personal monitoring of DBA vapor samples were collected on silica gel tubes using a low flow pump. Adipic, glutaric and succinic acids were separated by ion exchange chromatography followed by FID detection.

Adipic acid dust TWA samples are collected gravimetrically using 0.8 micron pore sized mixed cellulose ester (MCE) filters that are matched-weighted to within 50 micrograms. Matched-weight refers to two filters that are matched in weight and loaded into a 37 mm cassette. The top filter collects contaminants and the bottom filter serves as a control. After sampling, both filters are removed and weighed; the difference between weights is the total dust sample weight. LOGAN (Lognormal Analysis) is used for characterizing employee exposure to chemicals. LOGAN predicts exposure for an entire group in a given workplace based on a limited number of samples. LOGAN maintains that employee risk of overexposure is less than 5%.

Occupational Exposure to Dicarboxylic Acid Vapor During Manufacture				
Chemical	No. of Results	Avg. of TWA (mg/m^3)	Min. of Results (mg/m^3)	Max. of TWA (mg/m^3)
Adipic Acid	14	0.10	0.02	0.58
Glutaric Acid	14	0.13	0.01	0.21
Succinic Acid	13	0.11	0.01	0.15

Exposure to Adipic Acid Dust During Loading Operations				
People	No. of Results	Avg. of TWA (mg/m^3)	Min. of Results (mg/m^3)	Max. of TWA (mg/m^3)
8	25	0.5832	0.01	4.1475
16	14	2.26	<0.01	15.28

Exposure to Adipic Acid Dust by QA/QC Technical Personnel				
Chemical	No. of Results	Avg. of TWA (mg/m^3)	Min. of Results (mg/m^3)	Max. of TWA (mg/m^3)
16	3	0.10	<0.01	0.20